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Articulating the social responsibilities of translational science

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In recent funding calls, the National Center for Advancing Translational Sciences has shifted its focus from "translational research," which applies to studies in specific therapeutic areas, toward "translational science" interventions which aim to modify the system of translational discovery in the health sciences. To date, the social responsibilities of translational science have not been adequately articulated. In this paper, we argue that the ethical practice of translational science should include explicit social responsibilities that contribute to improved health outcomes and decreased disparities. Articulating social responsibilities specific to translational science is justified based on three of the field's foundational elements: (1) the social contract regarding public funding of research, (2) the goals of translational science, and (3) the increased risk of direct, indirect, and systemic harms from translational science, which involve system-level changes. We integrate social responsibilities into a framework which prioritizes developing relevant, usable, and sustainable innovations in translational science and provide three illustrative examples to demonstrate the practical application of this framework.

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Introduction

In recent decades, there have been numerous significant innovations in genomics, nanotechnology, personalized medicine, data science, and other fields within biomedical research. However, owing to challenges in translating findings into interventions that can reach patients and populations, the practical applications of these impressive achievements and their consequent impact on health outcomes are often underwhelming (Ioannidis, 2006; Fang and Casadevall, 2010; Mak et al., 2014; Seyhan, 2019). For example, the likelihood of success of phase 1 investigational drugs is 10.4% and has not increased over the last few decades (Hay et al., 2014). Even when a drug, device or intervention is deemed effective, the research environment is very different than practical clinical settings and poses significant difficulties in the dissemination, implementation, and scale-up of research products (Koorts et al., 2018; Mateo et al., 2022).

The field of translational research emerged in the 2000s to examine and ultimately reduce barriers that hinder research findings from being implemented in ways that improve patient and population health (Zerhouni, 2003; Zerhouni, 2005). It requires scientists to make earnest efforts to translate or disseminate their findings into clinical or population-level applications, rather than simply rewarding basic discovery (Solomon, 2015). The expectation that translational research will provide particular social benefits—hereafter referred to as the *social responsibility of translational science*—has been integrated into translational research narratives since the field's inception and throughout its institutionalization.

Historically the terms *translational research* and *translational science* have been used interchangeably. However, recently, the National Center for Advancing Clinical and Translational Sciences (NCATS) within the United States (US) National Institutes of Health (NIH) has worked to better define and distinguish these terms. *Translational research* is increasingly framed as research within a specific domain or therapeutic area. *Translational science*, on the other hand, has emerged as a set of practices which abstract the translational process from particular disease areas to develop interventions that can be applied to advance translational research goals across a range of therapeutic areas (Austin, 2018). Large information technology infrastructures/databases, the framework of "learning health systems," regulatory changes to facilitate speedier drug approval processes, and the advent of multi-site translational teams are some examples of this aim to more effectively deliver and improve research outputs, health outcomes, and thus social benefits. In the US, the approximately 60 NCATS research centers or "hubs" funded by Center for Translational Science Awards (CTSA) are now focusing on this broad meta-science view of translational science, which is sometimes called the "science of translation" (Department of Health and Human Services, 2021; NCATS, 2023).

In this paper, we articulate practical ethical considerations regarding the social responsibility of translational science to help translational researchers achieve the field's stated goals of producing innovations that improve health outcomes and decrease disparities. We argue that while improved health outcomes and decreased disparities are often explicitly stated goals of translational science, there is a failure to recognize these goals as social responsibilities that are particular to the field and require specific consideration for ethical practice. Instead, improved health outcomes and reduced disparities are often conflated with—or conceptualized as byproducts of—greater efficiency and innovation in the health sciences. However, improved population health outcomes and reduced disparities do not necessarily follow from faster discovery and translation (Morris et al., 2011). Indeed, sweeping statements about the potential benefits of translational science, while aspirational and virtuous, often fail to acknowledge and address how translational practices and discoveries will lead to actual and measurable social benefits (Burke et al., 2008). We thus argue that explicitly defining the goals of translational science as a set of social responsibilities that ought to be applied through specific ethical best practices would be more precise and effective in achieving the field's lofty aims of transforming scientific discovery to benefit society.

We first differentiate *translational research* from *translational science* and provide three case examples from the scientific literature to highlight the distinction. We then explore the positions of ethics scholars who have written about the ethics of *translational research* and highlight their shortcomings in considering recent conceptualizations of *translational science*. Although recent ethics scholarship concerned with translational discovery has considered ethical issues regarding social benefit and equitable application, this field remains both limited in scope and mainly applicable to research within specific therapeutic areas. Following this, we present our argument for recognizing the importance of the social responsibility of translational science, with reference to (1) how public funding for translational discovery creates a specific social contract, (2) the fundamental goals of translational science (including improved health outcomes and reduced health disparities), and (3) the duty to mitigate the potential risk of direct, indirect and systemic harms that could stem from translational science innovations. We demonstrate how key values of translational science—relevance, usability and sustainability—can be interpreted and applied to integrate social responsibility into translational science practice. Lastly, we highlight how differently positioned stakeholders should contribute to fulfilling the social responsibilities of translational science. Although this paper was developed based in part on US science policy, we believe that the final framework is also applicable to other jurisdictions internationally, given that translational science is a transnational phenomenon.

Defining translational research and translational science

Although discussions of translational research started in the 1990s, the framework took on more importance in the US in 2003 when NIH wrote its "Roadmap for Medical Research" which highlighted obstacles to translation, how this limited opportunities to improve health outcomes, and identified initiatives to reduce those barriers (Zerhouni, 2003). In 2012, NIH established NCATS to operationalize its commitment to translational science. NCATS's mission is to transform the translational process by supporting research institutes to establish the infrastructure and collaborative network throughout different fields of research and create interdisciplinary spaces (NCATS, 2022b). It has funded translational research projects as well as infrastructure through the CTSA network.

In the 2000s, translational research was often conceptualized as a unilinear process consisting of five translational domains: T0, when basic knowledge is translated to animal models; T1, when animal research is translated to human subjects; T2, when successful human trials research allows for the use of interventions with patients; T3, when treatments approved for patients become part of routine practice; and T4 when the translation of findings from routine clinical practice to improved community outcomes (Fort et al., 2017). If innovations do not bridge these translational stages, then there is a risk that benefits to patients and populations may not be realized. This unilinear conceptual model (from T0 towards T4),[1] has been criticized as an idealized and unrealistic model of science as opposed to more iterative, recursive, and multidirectional scientific processes (Schechter et al., 2004; Hait, 2005; Farroni and Carter, 2013).

Former NCATS director Christopher P. Austin (2018; 2021) draws from NCATS's definitions of key terms to make clear the distinctions between (1) the general idea of *translation* in scientific research, (2) *translational research* as a set of practices that aim to advance translational knowledge within a domain, and (3) *translational science* as a domain-agnostic area that works to understand and improve the processes that facilitate translational discovery. Following Austin and NCATS, we define domain-agnosticism in translational science as the broadening or de-contextualization of scientific inquiry in a manner that abstracts the translational process from a disease-specific area of inquiry towards processes and practices that apply across different domains. Similar definitions of translational science have been integrated in the most recent call for funding of CTSA institutions and will guide future developments in US translational science. Therefore, we adopt these definitions to provide conceptual clarity for our analysis regarding ethical issues in translational science specifically understood as a "disease-agnostic" or even "disease universal" form of interventional metascience that aims to improve the process of translational discovery and dissemination science for all translational stakeholders (Austin, 2018; Austin, 2021).[2]

We show that the ethical implications of developing translational science interventions—which operate at the systemic level—differ from those in domain-specific translational research. This is because translational science seeks to reshape and hasten the process of translational discovery by changing the scientific process itself—for example, by creating data infrastructures that allow for stages to be skipped or moved through much more quickly, or by developing tools to quicken the discovery or uptake of novel therapeutics. Because translational science often implies the modification of existing translational research frameworks along with altering basic approaches to discovery and dissemination, the ethical implications of translational science are both particular to this increasingly influential field and also wide-ranging with major downstream implications for biomedical research and health systems.

To better exemplify translational science, in Table 1, we describe three cases of translational science: (1) organs-on-a-chip, which aim to allow for more efficient pre-clinical toxicity analysis; (2) the field of translational data science (TDS), which aims to create new big data infrastructures and methods to facilitate complex cross-stage research; and (3) master protocols, which aim to explore multiple hypotheses simultaneously while requiring fewer human subjects and allowing for modifications over time as data is analyzed. These three empirical cases will be used throughout this article to highlight practical examples of translational science in practice.

Ethics of translational science

While not entirely applicable to ethical issues in disease-agnostic *translational science*, the development of ethical scholarship concerning *translational research* informs our thinking. The introduction of translational research as a concept in the health sciences prompted consideration of whether previously created guidance for the protection of human subjects, animal welfare, biosafety, and research integrity sufficed, or if new ethical frameworks were warranted.[3] We can draw several conclusions from shifts in ethicists' work about translational research to consider the social responsibilities of translational science. Guidelines created to manage ethical issues arising in the conduct of clinical and pre-clinical research focus on specific actions and decisions within research studies. Translational research requires that researchers and ethicists focus on linkages or relationships between research activities and their outcomes, in order to consider the broader range of implications for researchers, participants, communities, and society. This increased emphasis on applications of research to implementation created increased ethical responsibilities for researchers not only regarding human subject protections but also regarding peers, patients, and communities.

Ethics scholars critiqued the general "translational ethos" by underscoring various problems associated with specific types of outcome-based science such as stem cell research and genetic research (Hyun et al., 2008; Maienschein et al., 2008; Master and Özdemir, 2008; Sofaer and Eyal, 2010). Scholarship in the ethics of translational research has tended to focus on linear translational models from "bench to bedside," looking at issues particular to each step or between each step, which are often referred to as the "translational valleys" where findings fail to be operationalized in a subsequent stage (Butler, 2008; Sofaer and Eyal, 2010). To understand and address novel ethical issues in translational research, ethicists were integrated into the translational process to foster ethical reflection in translational activities (Farroni and Carter, 2013). Research ethics consultation services (RECS) were a required component of the initial CTSA funded institutes to ensure that researchers could avail themselves of as-needed research ethics expertize (McCormick et al., 2013; Cho et al., 2015).

Ethicists also undertook further studies under a translational banner. This included studies to reduce regulatory barriers while also addressing potential ethical issues raised by multi-site collaborations (Check et al., 2013; Klitzman et al., 2017; Resnik et al., 2018). With the increased emphasis on implementation science in translational science, new ethical issues were identified when translating evidence into practice, often related to engagement with communities (Damschroder et al., 2009; Department of Health and Human Services, 2021). Engagement with communities and patient organizations has also forced ethicists to look beyond the human subject and prioritize group-level considerations, thus broadening notions of justice (Ross et al., 2010). The inclusion of relevant stakeholders throughout the research process was justified and welcomed to ensure acceptability of interventions, and to address problems of diversity in recruitment and retention (Holzer, 2012). Trust between researchers and the public was also considered a possible outcome of greater community engagement (Holzer et al., 2014).

Because translational science operates in a domain-agnostic fashion that is meant to be applicable across a wide range of fields, the ethical frameworks that guide it ought not rely solely on approaches that were developed for disease or domain-specific areas of translational research. Although broader justice concerns have been discussed in certain translational research domains, notions of social responsibility in translational science have never been sufficiently articulated within such ethical frameworks. This next section defines this notion of social responsibility and determines reasons why it should be integrated in the ethics frameworks.

The social responsibility of translational science

In this section we will first consider the general concept of social responsibility in scholarly literature, and then review its importance, interpretation, and justification within the field of translational science. The term "social responsibility" has been defined in many different ways. Numerous scholars have argued that scientists should address the implications of their work for society (Russell, 1960a; Shrader-Frechette, 1994; Resnik and Elliott, 2016; Elliott, 2017; Kobylarek, 2019). Debates regarding the potential unforeseen negative impacts of scientific developments have been central regarding the development of weapons of mass

Table 1 Translational science cases.

Case Names	Case Description
Organs-on-a-chip	Organs-on-a-chip are micro-engineered devices using tissues from different cell types that interact in a complex microfluidic environment. They allow researchers to study molecular and cellular-scale activities that underlie human organ function and mimic disease states; this biotechnology may also be used to test novel therapeutic agents in vitro. Application of this technology may expand further beyond its current use in physiological studies, morphogenesis studies, pathology, pathophysiology, pharmacology, and toxicity assessment (Ashammakhi et al., 2019). Organs-on-a-chip represent an important translational science innovation because they claim to be more effective and efficient than traditional in vitro model experiments (Ronaldson-Bouchard and Vunjak-Novakovic, 2018). The loftier goal of creating a body-on-a-chip that would result in less human subject use is aspirational at this time.
Translational Data Science	Translational Data Science (TDS) is a set of methods, values, and infrastructures rooted in big data approaches that combine principles of translational science and data science to create new opportunities for research and to accelerate the pace of discovery across translational stages. The TDS concept was first fully articulated during a 2017 workshop in Chicago sponsored by the National Science Foundation (NSF) (Baru et al., 2017). Contributions to TDS take two primary forms: (1) using translational datasets to develop new methods in data science and (2) problem solving by applying data science principles to address issues that have important impacts on human health or social welfare (Baru et al., 2017). Innovations in TDS can take the form of developing methods, big datasets, or approaches that fulfill one or both of these aims. TDS therefore contributes to basic advances in domain-agnostic translational science and data science as well as to applications of data science approaches that enhance the process of translational research in specific disease areas or domains (Ribes et al., 2019).
Master Protocols	Master protocols have been described as an "evolutionary shift" in clinical trial methodology for new cancer therapeutics (Redman and Allegra 2015). Master protocols use genomic sequencing to evaluate multiple hypotheses of sub-studies concurrently. Master protocols can be "umbrella," "basket," or "platform" trials. Umbrella trials are focused on a single disease but compare multiple targeted therapies; basket trials are focused on multiple diseases that have a molecular alteration in common; platform trials combine features of both and may continue with modifications/alterations as necessary (i.e., no definitive endpoint) (Lu et al., 2021). By combining genetic screening/genomic sequencing, these novel trial methodologies and new statistical analyses allow for concentrated effort to yield greater knowledge while burdening fewer participants. Additionally, platform trials are often conducted by multiple sponsors who then share in resource use to achieve outcomes (Lu et al., 2021). Master protocols are able to differentiate exceptional responders from their sub studies —participants in a group who respond to an intervention where others don't, and thus may have genetic profiles of interest for further intervention development (Hirakawa et al., 2018).

destruction (Russell and Einstein 1955), the long-term health impacts of agricultural pesticides such as Dichlorodiphenyltrichloroethane (DDT) (Commoner, 1970; Carson, 2002), and the long-term effects of gene editing (Baylis, 2019). However, many scientific advances notorious for leading to harms have also enabled the development of very beneficial health-based interventions that reshaped healthcare in the 20th century. For example, the atomic science used to create nuclear weapons also contributed to medical imaging (Masco, 2021). This ability to create technoscientific innovations that can result in unforeseen benefits and harms to individuals and populations is defined as "dual-use."

The concept of dual-use is contentious as it is often too broad for meaningful policy applications since most technoscientific knowledge can be misused to create harm (Husbands, 2018). To avoid overregulation, governance regarding dual-use has applied to specific experimentation in synthetic biology that may create significant long-term harm such as experiments that include select agents (e.g., Ebola, Anthrax), gain-of-function in synthetic biology, or work with potential pandemic pathogens (Imperiale and Casadevall, 2015). Ethical frameworks regarding dual-use often rely on concepts of prevention, risk mitigation, and precautionary reasoning (Kuhlau et al., 2011; Kelle, 2013). The sociopolitical values of security and protection of national security have been enmeshed in dual-use governance linking scientific responsibility and policing within the "ethicalization" of dual-use (Rychnovská, 2016).

Although the social responsibility of scientists has been recognized and integrated into dual-use debates, it is often interpreted as a negative obligation to avoid creating harm to future populations as opposed to a positive obligation to increase social benefit through innovation. Definitions that include the positive obligations and broader scope of social responsibility of scientists is much less clear (Pimple, 2002). Mark S. Frankel from the American Association for the Advancement of Science (AAAS) argued that scientists had "internal" (epistemic) social responsibilities as well as external responsibilities (Frankel, 2012). Internal responsibilities relate to the professional obligations of scientists to create "good science" which include standards of scientific practices also referred to as epistemic values (rigor, reproducibility, bias reduction). The external responsibilities or what is owed to society is less discussed in the scholarly literature. Wyndham and colleagues (2015) conducted a survey funded by the AAAS amongst 2153 researchers to better understand the perspectives of scientists, engineers and health professionals regarding their perspectives on social responsibility. Researchers were to rate the importance of different socially responsible behaviors. Topics deemed most important included risk minimization, reporting misconduct, explaining research to the public, and serving in advisory role in public arena (Wyndham et al., 2015).

In Wyndham's study, managing the risk of harm remains most important but other aspects of governance such as including the public are also valued. Over the last few decades, scholars have highlighted the need to think beyond the management of risk, which has been central to the dual-use ethical dilemmas that too often limit the debate to specific experiments (Edwards et al., 2014). Rather, the dual-use debate may include ways to govern innovation's broader purpose and goals. Some scholars have included responding to social problems by prioritizing them at the onset of research, an obligation to answer to social needs, or by treating science and society as co-constructed (Jasanoff, 2004; Glerup and Horst, 2014). Similarly, Stilgoe and colleagues (2013) introduce a responsible research innovation framework that focuses on dimensions of anticipation, reflexivity, inclusion, and responsiveness. These dimensions imply consideration and

anticipation of various risks and put significant emphasis on inclusion of different actors such as end-users within scientific governance and development while also being responsive to public values or preferences.

This idea of expanding the goals and impact of science to increase the social benefit of science is particularly important and central to the already existing goals of translational science. The field of translational science was created to modify the system, techniques, and tools used in the health sciences in a way to increase benefits to people. Although the initial goal was to increase the speed of science in an efficiency focused model, the broader idea of translational science requires us to reduce barriers that may be limiting the application of science to the benefit of society (Zerhouni and Alving, 2006). Understanding notions of "health improvement" in a commercial lens could lead to the development of technologically advanced and expensive interventions that might not be easily accessible due to price, thus not aligning with the needs or practical realities of communities. One could argue that such high-tech commercial development may improve health outcomes of a small group of individuals who can afford such services. However, improving the health of those with access to high-quality insurance and greater socio-economic privilege without also improving the health of those with fewer resources and social advantage would necessarily lead to worsened population health disparities. This has arguably occurred during the uneven global rollout of curative antivirals for hepatitis C, a process nonetheless characterized by Manns and Maasoumy (2022, 533) as "a role model for successful biomedical and translational research" (Millman et al., 2017; Thompson et al., 2022).

We define the central social responsibility of translational science to be creating innovations that lead to (1) improved health outcomes and (2) decreased health disparities. The details and justification of our definition of social responsibility will be developed further. However, our definition of social responsibility assumes a general familiarity with egalitarian theories of justice, with similarities to Alex John London who argues that science should have an important social role in advancing basic interests of the public (London, 2021).[4] This is not to imply that there are no other social responsibilities to be considered. Arguments supporting the claim for greater social responsibility in science beyond the translational enterprise include general moral duties such as avoiding causing harm to others, the obligation to help others, and the obligation to benefit the public in research funded by public dollars (Resnik and Elliott, 2016). General social responsibilities that apply to all scientists or professionals should also apply to translational science. Moreover, certain scientists may also have specific responsibilities due to their context, country, and the particular impact of their research.

Specific arguments which underscore the importance of social responsibility in translational science are evidenced through the social contract regarding public research funding, the fundamental goals of translational science, and the duty to mitigate potential risks linked to translational science. Although these foundational elements do overlap with broader discussions of social responsibility, their application to translational science provides specific insights into the ways that this domain-agnostic field can improve health outcomes and reduce disparities.

Social contract regarding public research funding. As previously mentioned, long before the emergence of translational science, public funding of research implied that scientists have specific social responsibilities (Russell, 1960b). Knowledge is generally considered to be either intrinsically valuable or at the very least instrumentally valuable (Kirschenmann, 2001). Although intrinsic value with little or no instrumental or practical value may be acceptable for certain types of research, it is explicitly not acceptable for translational health research, which is intended to yield social benefit. When social benefits failed to sufficiently materialize as practical social goods that increased the health of populations, translational science attempted to redefine the "social contract" between science and society to promise results on quicker timeframes (Maienschein et al., 2008).[5]

To adequately change science, an inclusive system-based approach is needed, which includes health funders. Pierson and Millum (2018) suggest that all research health funders have the obligation to maximize global social value. According to these authors, social value is a function not only of maximization of expected benefit but should also help those with the lowest expected well-being over a lifetime.[6] In this view, the social responsibility of funders includes *(1) improved health outcomes and (2) decreased health disparities*. If health research resources are reallocated in a manner to maximize social value and instill a notion of fairness and equity, and if public funding requires research stakeholders to explicitly follow such values, it then follows that research stakeholders must further that mission.

In Table 1 presented earlier, three different innovations were outlined as examples of translational science. The first example—the development of organs-on-a-chip—is presently central to two publicly funded NCATS programs that aim to create more reliable, reproducible and automated chip based microphysiological systems (Low et al., 2021). However, scaling up the technology may not necessarily result in products accessible to laboratories throughout the world, such as those in low-to-middle income countries (LMICs). As a consequence of this, organs-on-a-chip may not be validated to test medications that would be most relevant to health conditions disproportionately faced by individuals living in LMICs. However, if we include both goals of improved health outcomes and decreased disparities, scientists should be including the range of implications related to cost, access, and fairness when developing this technology. Similarly, the third example—the development of master protocols - allows multiple molecular targets to be studied simultaneously using fewer human subjects. This approach could be applied simply in the interest of improved efficiency. However, master protocols can differentiate exceptional responders from their sub studies and therefore focus on groups that may otherwise have received little attention (Hirakawa et al., 2018). Similarly, more informative subpopulation analyses are possible under master protocols. If translational science prioritizes concurrently improving health outcomes and reducing disparities, studying such subpopulations may reduce certain inequities.

The literature on translational science underscores basic contradictions regarding the funding and practical implementation of translational science interventions. In the US, translational science aims to accelerate the discovery of advanced therapeutics in a for-profit system that relies on inequitably organized markets and health systems to distribute care (Waitzkin, 2000). This structural contradiction in the aims of translational discovery is a constitutive feature of translational science that entities like NIH cannot solve alone. However, research priorities, approaches, and dissemination can and should follow the social responsibilities of the translational enterprise. For this to happen, addressing contradictions between innovation in research and applicability to populations should be a central preoccupation in discussions about the social responsibility of translational endeavors and in accompanying ethics frameworks. We believe the criteria as we develop them below can help translational scientists better address issues related to social responsibility.

The goals of translational science related to improved health outcomes and decreased health disparities. Traditional research may aim to understand human health issues and important mechanistic phenomena linked to health to develop innovative ways to cure diseases. Historically, the implementation and dissemination of research was seen as a separate endeavor that overlapped significantly with access to care, health system decisions, and public health more broadly (Solomon, 2015). This differentiation between research and clinical practice has its roots in the Nuremberg Code and the Belmont Report. However, the clinical/research distinction has since been criticized as outmoded given the emergence of counterexamples such as learning healthcare systems in the research and medical landscape or the use of experimental drugs in clinical care in expanded access programs. Other scholars have highlighted how the distinction between research and clinical practice has always been problematic (London, 2021).

"Efficiency" is typically invoked when discussing speed and innovation. However, speed and innovation alone are not the only problems of translation and do not necessarily address or ensure the social responsibility of improving population health and decreasing disparities. For example, high-tech innovations in genetic and genomic research were often hyped as increasing health for all through novel and accessible means such as direct-to-consumer genetic testing (Hedgecoe and Martin, 2003).While this mode of testing may indeed reach more people, and may be scientifically relevant, it may well have limited clinical utility and even less public health applications. This is not to infer that the genetic information itself is inherently problematic, but rather that its impact on the health of populations may often be negligible especially when considering health disparities. In their book *Achieving Justice in Genomic Translation*, Wylie Burke (2011, 6) and colleagues note that

> Paradoxically an overemphasis on improving the efficiency of translation may fail to benefit individuals and families, particular groups, or even public health generally. In the worst-case scenarios, such investments, could bring harm to the very populations most in need of benefit—populations already suffering from health disparities—if not directly, then through opportunity costs of distracting funding and resources to these nonbeneficial technologies.

In sum, many biotechnological innovations may have been more efficient in increasing the health of those most fortunate. However, these interventions were likely to remain inaccessible to those without means of payment.

If efficiency is measured solely in terms of speed and innovation, Burke et al. (2011) are right that efficiency of translation can indeed fall short of expectations and create extremely inequitable outcomes. If efficient "good science" is limited to values internal to the system—speed, accuracy, rigor, completeness—we might create innovative knowledge with limited or highly inequitable social applications, which is contrary to the mission of translational science.

For example, as shown in Table 1, researchers have developed TDS innovations to support applications of data science in translational research projects and to use translational research data to develop novel methods in data science (Baru et al., 2017). This approach has often been justified in the name of efficiency by speeding up the pace of innovation and creating integrated data infrastructures or "data commons" to improve timely research outputs and to support novel forms of collaboration (Grossman et al., 2021; O'Hara et al., 2022). However, moving too quickly in the name of collaboration to address health problems can potentially worsen inequities. During the COVID-19 pandemic, for example, the issue of algorithmic bias arose frequently in relation to interventions and applications that were developed in short timeframes using datasets that potentially reinforced existing inequities or assumptions about particular groups, especially racial and ethnic minorities (Leslie et al., 2021; Delgado et al., 2022). Ensuring that the social responsibilities of translational science are considered alongside "efficiency" and related outcomes may generate better science that is relevant and useful to end-users while also being sustainable and deliverable to patients.

In asserting improved health outcomes and improved population health as goals, translational science underscores the integration of clinical research, medical practice and public health practice in the explicit pursuit of social benefit. However, at the inception of translational research there seemed to be a limited focus on fair distribution of health outcomes, health disparities, or improving equity. Issues in this area were highlighted when inequities were demonstrably increased by translational researchers (Yousefi Nooraie et al., 2022).

However, NCATS has more recently prioritized initiatives that address unmet needs, defined as scientific needs as well as patient and population needs ((NCATS, 2022). In recent funding calls, NCATS does mention that one of its goals is to decrease health inequities through partnerships with communities (Department of Health and Human Services, 2021); however, broader outcome-based discussions regarding long term health equity remain scant. Community engagement groups and implementation researchers have also highlighted the system's obligation to give a higher priority to health equity by reducing, or at least not increasing, disparities in downstream applications of translational research (Brownson et al., 2021).

A main challenge at hand is that the extent to which research may improve health outcomes and reduce disparities is dependent on the effectiveness of a nation's underlying healthcare system (Coller, 2018). In other words, if there is no pathway for individuals and populations to access goods developed through translational research, the goal of improving health outcomes and reducing disparities will remain unfulfilled. While beyond the scope of this paper, we emphasize the need for meaningful policy reforms that will integrate the goals of translational science into an improved health system explicitly structured around ensuring universal access to high-quality care.

Risks of translational science. Social responsibility in science is the subject of enduring debate focused both on responsibilities inherent in undertaking scientific activities (procedural concerns that address the "how" of science) (Harding, 1986) and the responsibilities attendant to the outcomes of one's work (substantive concerns) (Russell, 1960a). Translational science aims to modify the system of translation which may in turn alter and increase certain risks of harm in at least four ways.

Firstly, the effects of applying a new translational science intervention may be so far downstream that the impact is unclear or remains undefined. Since translational science implies systemic changes, the results of its application may be measured in terms of modifications to translational projects and their contributions downstream. The issues regarding distance from practical application are similar to those in TDS. When identifying predictors in large amounts of data or configuring a system that pulls data from various sources to create a more substantial dataset, researchers make technological and data contributions to the work, but may not be able to imagine all the downstream impacts. The dilution or lack of contextual specificity makes it challenging to accurately determine and consider the potential impacts of translational science interventions. The disease-agnostic process often reduces discussion

of values, preferences, priorities of populations, and other contextual concerns, therefore increasing risks mainly for minoritized populations given the systemic injustices entrenched in the scientific process.

Secondly, oversight bodies such as Institutional Review Boards (IRBs)[7] or Institutional Animal Care and Use Committees were created and trained to look at disease-specific research projects and guided by regulation, that is not responsive to the kind of systemic interventions promoted by translational science. For example, if bioinformatics and organs-on-a-chip research were to replace animal research to improve the system and reduce the number of animals used for research, the IRB would be required to use different types of data to evaluate whether or not preclinical data is sufficient to start human studies. Although this new approach may be more effective in the long term, governing bodies may need to learn different ways of assessing the types of data to protect human subjects. IRBs will need to assess the translational research projects modified by translational science interventions that have altered the system. In so doing, IRBs would be called upon to consider the impact of the loss of certain information which is beyond established practice and their expertize.

It may be argued that there is heavy-handed oversight of risks to humans and that already cumbersome governance structures should not be made more burdensome. However, translational science stakeholders need to understand that translational science risks are particular and distinct and may require different types of assessment. Indeed, a major goal of some translational science interventions is to change the regulatory environment for biomedical research, which has the potential of accelerating the introduction of riskier research. Greater or different types of risks to human subjects might occur simply because the process itself is evolving and not altogether predictable. The potential multi-level risks of translational science are seldom discussed; the emphasis on improved processes has overshadowed questions around potential harms (Austin, 2018; Austin, 2021).

Third, the scope of translational science is broad and includes discovery, development, and dissemination in complex environments where there are significant commercial, political, and social interests at play (Robinson, 2019). In past research more broadly, significant bias has resulted from commercial interests driving research agendas (Krimsky, 2003). For example, Sismondo (2008; 2009) and Sismondo and Doucet (2010) have described the various ways in which industry has infiltrated the pharmaceutical research pathway and publication process by hiring independent scholars, statisticians and medical writers that would release pro-industry publications with the goal of increasing commercial value of research. Similar tactics were used to support the tobacco industry and develop evidence that can be used to counter environmental tobacco smoke policies (Muggli et al., 2001). Given the applied nature of translational science, commercial interests will often be involved in bringing health interventions to market. This may sway science towards a political or commercial agenda that is contrary to our explicit goals in articulating the social responsibilities of translational science to (1) improve health outcomes and (2) decrease health disparities. As highlighted in previous examples, interests may also bias important scientific norms including rigor, validity, transparency, and completeness.

Fourth, a major risk of translational science is potentially reducing the methodological variability of translational pathways. Evaluating scientific processes to find efficiencies, old methods, skills, forms of expertize, and resources to replace them with novel translational ones could result in losing certain benefits that older systems offered. Studies using older methods of a less novel system would likely not attract as much funding. In sum, prioritizing newer and more efficient processes may increase the speed of discovery, but it could be challenging to determine with accuracy the long-term risks that process or system-based translational science modifications may create. Potentially reducing the diversity of methods and practices used in scientific research may reduce diversity of thought, expertize, or specific skillsets (Hess, 2011). The loss of a pluralistic innovation processes in favor of selecting the newest and most efficient approaches could even negatively impact scientific discovery, capacity for innovation, training, and downstream applications (Hess, 1997; Hess, 2011).

The practical articulation of social responsibilities of translational science

In this section we apply the criteria of relevance, usability, and sustainability to integrate social responsibility into translational science. We begin by discussing the rational for these criteria which include their common usage in scholarly literature related to translational science as well as their ease of integration in practice. We then demonstrate how these can be effective guiding criteria to (1) *improve health outcomes* and (2) *decrease health disparities*. The novelty of this approach is the integration of social responsibility goals (improved health outcomes and reduced health disparities) into a normative ethics framework to enable application in practice.

At the outset of this research process, the authors reviewed the ethics and policy related scholarly literatures about translational research and science and looked for concepts with normative force that could be a vehicle for social responsibility and identified relevance, usability and viability. As mentioned by Lieke Van Der Scheer and colleagues (2017, 226): "The discourse concerning [translational research] is explicitly normative, implying that good biomedical research aims for values such as innovations that are *relevant* for and *useful* in the clinic and are also *economically viable*" (emphasis added by authors of this manuscript). Across translational literatures, there is ongoing debate about how translational research ought to be relevant (Marincola, 2007; Glasgow and Chambers, 2012; van der Scheer et al., 2017) and useful in clinical application or public health interventions (Califf and Berglund, 2010; Khodyakov et al., 2016; Austin, 2021), while also promoting sustainable systems to ensure durable partnerships, programs and health impact (Graham et al., 2016; Yousefi Nooraie et al., 2022). Notably, discussions about such criteria have often been vague. They have not been used in the service of social responsibility or any ethical framework. This article aims to clarify their use as central ethical dimensions of social responsibility in translational science.

The articulation of social responsibility through relevance, usability and sustainability will provide a shared vocabulary as well as goals and common points of reference that stakeholders throughout the system may further discuss. In previous sections, we have argued that the translational science enterprise has a social responsibility, which is a system-level argument. In practice, stakeholders will need to discuss, disclose, and monitor issues related to relevance, usability, and sustainability in order to collaborate in promoting socially responsible innovation. We have defined relevance, usability and sustainability in Table 2 to provide conceptual clarity and further discuss their application throughout the next three sub-sections. The integration and articulation of social responsibility through translational science's own criteria of success—relevance, usability and sustainability—helps shift the focus of research from a project that is solely a technical scientific endeavor (seemingly value-free) to a project that includes increased explicit social benefits (improved health outcomes and decreased disparities).

Table 2 Definition of relevance, usability and sustainability.

Criteria	Definition
Relevance	Research should apply to the health needs of at least one stakeholder with the goal of increasing health outcomes. Stakeholders may include a group of patients in clinical practice, a community or population (or sub-group of a population) or a researcher in the translational process that will create downstream impact on health outcomes. When looking at the system of science—which includes the relevance of all studies—there should be consideration for equitable distribution. Questions of interest: • Who are the end users of this research? • Can I increase the downstream impact of this research with emphasis on those most in need?
Usability	Research should assess the practical considerations of the range of stakeholders. Practical considerations include costs of application, complexity of use, and priorities of stakeholders. Usability of innovation is also intertwined with values of stakeholders. Usability also includes the downstream implications that translational science has on translational research interventions. Usability is also required for adequate implementation to evaluate the limitations of usability. Questions of interest: • What are downstream expected costs for various stakeholders? • Will the downstream translational intervention decrease or increase accessibility to interventions? • What are the values of expected stakeholders and will downstream research conflict with such values?
Sustainability	Long term viability of translational research infrastructure as well including the viability of research application within the regulatory, economic, social and environmental context. Questions of interest: • Can the translational system develop translational science interventions that will be viable and usable in the long term? • Will resources and infrastructure be sufficient to ensure long term and ongoing benefit with emphasis on the downstream impact on those most in need? • Can the intended beneficiaries of the innovation equitably access it (e.g., patients or users of a new tool designed for use in biomedical research)?

Relevance. Notions of relevance can be defined as *social relevance* which impacts society directly or *scientific relevance* where researchers increase understanding of a disease or process (Shaw and Elger, 2013). Clinical research has already started looking at relevance in terms of social, scientific and clinical value (Emanuel et al., 2000). Greater emphasis on the application of social responsibility to this criterion will require that the system of science consider the end-user(s) and beneficiaries of translational science innovations and downstream impact. In this framework, we will limit the notion of "relevance" to the identification of the end-user which may include any stakeholder in the system of science. For instance, a translational science intervention in bioinformatics may decrease the use of animals in preclinical work. It may also benefit scientists' work by becoming more accurate and creating more effective downstream translational science innovations for specific populations. Social relevance requires stakeholders to think about who this research will benefit and how. The translational science innovation system should be distributing funding and research capacity so as to increase social benefit in ways that improve health outcomes and decrease health disparities.

Funding agencies have responsibilities to make sure that funding is distributed to maximize benefits and to reduce disparities. If scientists were more explicit about the stakeholders that would benefit from translational innovations, funders could also distribute dollars in ways that improve health outcomes while also decreasing disparities. Recently, NCATS (2022) has explicitly highlighted the importance of prioritizing initiatives that address unmet needs, including those of scientists as well as patients and populations. To do so—and thus to fulfill the social responsibilities of translational science—translational scientists must identify who their application could benefit downstream when possible.

Usability/accessibility. Even if health research may be of relevance to an end-user, that individual may not use the intervention for various reasons such as access, choice, or convenience. Research stakeholders must carefully assess usability considerations. This would involve such practical considerations as costs and access of application or treatment, complexity of use, and the values and priorities of end-users. In the translational science space, one main end-user is the translational researcher who will use the translational science intervention. For example, in the case of organs-on-a-chip in Table 1, translational researchers will be using a translational science innovation for various purposes, such as toxicology assessment within a domain. If the chip is too expensive or complicated to access, the success of this intervention could be limited. Moreover, by monitoring and assessing the use of chips by translational researchers, we could determine which communities of patients are more likely to benefit from this technology and attempt to assess future needs if certain populations are not being served.

Usability of innovation is intertwined with values of intended users in their respective communities. Although usability may be difficult to define for some upstream translational science applications, this may not always be the case. For example, during the COVID-19 pandemic, researchers were quick to innovate and carry out the biomedical and bench work necessary to develop and produce vaccines for broad distribution. For various reasons, vaccine hesitancy significantly impacted the desired outcomes; there were also practical issues that limited the initial rollout of COVID-19 vaccination such as logistics, storage in cold temperatures, vaccine stability, and intellectual property frameworks that effectively blocked access for many LMICs (Erfani et al., 2021). To reduce some of these issues in future vaccine implementation, the creation of microarray patches provides a needle-free technology that help with issues of transport and storage. Increased ease of use, safety in administration, thermostability, and pain-reduction are arguments in favor of this technology that are often mentioned as ideal for low resource settings (Peyraud et al., 2019). The development of effective and accessible vaccine platforms is acknowledged to have had great potential public health benefit.

Appreciating limitations of access is particularly important where a translational science intervention yields costly end-products. This is not to discredit or discourage the development of expensive biotechnologies, methods, or compounds; rather, it is to recognize that they might not be optimal in improving

population health outcomes or reduce disparities. To address this, the translational science system could provide more effective funding redistribution when translational interventions are shown to yield improved health outcomes and decreased disparities.

Sustainability of research to stakeholders. Generally, improvements in health outcomes require repeated or extended use of an intervention. Translational science introduces changes to the system of science that may be costly and unaffordable; so, various stakeholders (mainly funders and researchers) should make sure that any modifications are viable in the long term. Entities ought to determine at the outset whether resources needed to ensure continued use of the system are finite, reusable, costly or morally challenging. This is particularly important to consider when assessing interventions that require commercial sponsorship, given that profit-oriented pricing tends to make interventions less accessible.

Researchers should also ask themselves and potential commercialization partners if the products of scientific development are sustainable and can be brought to market in an accessible manner to create long term benefits to the greatest number of people. For example, the development of a new expensive pharmaceutical compound may be of great scientific and medical worth. However, they may have limited sustainability because they offer only short-lived protections at significant costs when compared to the longer-term protection of vaccination at more affordable costs. Limitations regarding sustainability along these lines were significant when SARS-CoV-2 evolution quickly rendered monoclonal antibodies ineffective as a medical countermeasure during the COVID-19 pandemic (Liu et al., 2022; Planas et al., 2022).

Sustainability is also shaped by markets. In the US's current system of privatized healthcare, once a product has the potential to improve health outcomes, stakeholders must be able to cover the costs of production and bringing it market (Robinson, 2019). This may well be part of translational science that requires heath policy reforms designed to make payment for healthcare equitable and even to drive state investment into commercializing "unprofitable" interventions. Health policy modifications may also be required in relation to the translational system given potential for downstream impact.

In the translational science literature, there have been suggestions to create infrastructures that would yield better clinical trial outcomes. For example, London and Kimmelman (2019) have promoted a clinical trial portfolio approach. They suggest that basing drug approval decisions on one or few studies may yield only partial results regarding risks and benefits. However, if researchers brought together clinical trials with different indications for the same drug, they could more appropriately assess the broader risks and benefits of such drugs. The organization of studies in a comparable manner to increased social benefit will require well-funded and supported translational science infrastructures designed to provide portfolio support.

Fulfilling the social responsibilities of translational science will require coordinated action by many stakeholders. Key groups include investigators, evaluators, trainees, participants, research personnel, institutions, funding agencies, regulatory agencies, patients, biotechnology firms, and civil society actors. Although the obligations of different actors in the translational ecology vary depending on their position, role, and influence, they often must work in collaboration to ensure that the social responsibilities of translational science are achieved. Table 3 provides a taxonomy of stakeholders in translational science along with a discussion of the social responsibilities of each group.

Table 3 shows how the social responsibilities of translational science must be enacted as a set of relational values between key stakeholders who are differently positioned within the larger translational ecology. Therefore, while all actors and institutions in translational science have some power, those with more power have elevated obligations to ensure that the field's social responsibilities are fulfilled.

Conclusion

This paper argues that the social responsibility of translational science can best be fulfilled by centering the field's commitments to developing interventions that are *useful*, *sustainable*, and *relevant* to the task of domain-specific translational research. By developing domain-agnostic interventions to hasten the pace of sustainable and relevant translational discoveries, translational science stands to have greater social impact than many domain-specific projects, thus fulfilling its overall goals, mission, and social responsibilities. However, the risks of translational science are often wide-reaching since translational science calls for broad systemic changes to the scientific process itself or modes of

Table 3 The social responsibilities of key stakeholder groups in translational science.

Funders and Policymaking Institutions, including Congress, NCATS, other NIH institutes and centers, and additional entities that shape the direction of translational science can set priorities that recognize the field's social responsibilities. Congress and state governments should create supportive regulatory environments along with state-owned enterprises that can enable the commercialization of translational discoveries in ways that accelerate and maximize the reach of interventions that improve health outcomes, reduce disparities, and are broadly accessible and acceptable.
Organizations such as universities, professional organizations, research institutes, biotechnology firms, CTSA institutions, and other entities that support translational science can create environments where these endeavors can flourish while fulfilling the field's social responsibilities. Commercial organizations bear a particular burden to ensure that interventions make their way to all who need them, rather than only to those who can afford them. While commercialization is vital to the success of many interventions, health equity considerations ought to be placed before profit. This is particularly true because, at some point, all translational discoveries have benefitted from public funding (Robinson, 2019).
Translational teams are a primary organizational unit in translational science; if the integrity of a team cannot be sustained, the science produced by that team is likely to suffer (Rolland et al., 2021). For example, improving team dynamics is recognized as a tool to increase effective data management, psychological safety of team members, and to enhance reproducibility and broader research integrity concerns (Bisbey et al., 2021; Kotarba et al., 2023).
Individual translational scientists are often structurally disempowered, especially in team environments at highly regulated research institutions with funding constraints. In other words, the impact that an individual scientist has over the translational system may seem limited. However, our analysis suggests that translational scientists have a higher burden of social responsibility than other health sciences researchers. This is true because of the domain-agnostic nature of translational science and the potential downstream impacts of translational discoveries across domains. Therefore, translational scientists should work with their teams, organizations, funders, and professional associations to maximize social responsibility by producing interventions that improve health outcomes and reduce disparities.

discovery, development, and implementation. Therefore, in creating translational science interventions, stakeholders ought to center how the broad scope and wide applicability of many domain-agnostic interventions can potentially elevate or amplify risks.

The shared social responsibilities of translational science are weighty, manifold, and distributed unevenly across the various entities that make up and govern this field. The scope and breadth of the field's social responsibility is such largely because translational science carries all the social responsibilities of science in general, of the health sciences in particular, of domain-specific translational research, and then also creates its own specific social responsibilities that stem from the move toward domain-agnosticism in translational science. This move toward changing the translational process itself raises the ethical stakes of translational science higher than that of many other areas of the health sciences. Integration of bioethics, humanities and social science researchers within translational science teams can assist with the implementation of the social responsibility framework. A similar argument has been made by Mark A. Rothstein (2023) who has emphasized the importance of integrating bioethics in translational sciences which he coins "translational bioethics." More specifically, he argued that the social and political factors surrounding research innovation can create barriers to implementation as seen with the case of COVID-19 vaccine hesitancy. To reduce such barriers, Rothstein argues that translational bioethicists should be tasked to understand the ethical issues surrounding innovation as well as the broader social implications of research. The social responsibility framework presented in this manuscript adds a more practical application to Rothstein's argument by clearly articulating social responsibilities in the ethical conduct of research in translational sciences.

At a time when translational approaches are becoming central to an increasing number of health sciences fields, and where translational science increasingly aims to hasten the pace of discovery across domains by abstracting the process of translation away from specific therapeutic areas to affect core aspects of the process of scientific discovery, it is due time for translational science to take stock of its specific social responsibilities. We hope that our guiding criteria have helped to clarify not only what those social responsibilities are, but also how they manifest in practice and how they can be better achieved in future translational science activities. As health sciences funders begin to build the policy mechanisms that will carry forward the next era of translational discovery—and as organizations, scientific teams, and individual scientists respond to calls put out by funders—we hope that we have aided in placing social responsibility at the center of the ambitious and laudable goals of translational science.

Data availability

Data sharing is not applicable to this research as no data were generated or analyzed.

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Notes

1 Certain scholars conceptualize the translational stages slightly differently adding a fifth translational step that includes translation to global communities which includes change in policies and social systems (Graham et al., 2016).

2 On the emergence of this kind of "domain agnostic" or "domain independent" approach in data science, which notably emerged as a field in temporal alignment with translational science during the 2010s, see Ribes et al. (2019). Ribes et al. (2019)'s analysis of what they call "the logic of domains" and domain-agnosticism in data science informs our analysis of the increasing focus on disease-agnostic approaches in translational science.

3 Clinical human subject research is highly debated in research ethics both nationally and internationally and there is a significant body of guidelines, principles, processes and frameworks specific to human subject research. In the U.S., guidelines such as the Belmont report and the Common Rule aim to protect participants rights, safety and welfare (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979; US Department for Health and Human Services et al., 2001). There are also regulations that extend beyond human subject issues to address animal welfare and use in research (Animal Welfare Act, 2022), biosafety as well as a range of research integrity considerations such as misconduct, conflict or interest, reproducibility, and dual-use.

4 In his book titled "For the Common Good: Philosophical Foundations of Research Ethics" Alexander London generally considers broader notions of science although he does sometimes comment on interventions that are considered translational science like the learning health system (London, 2021).

5 The notion of "social contract" has been developed by political philosophers including John Locke and Jean-Jacques Rousseau. The intent of these political philosophers was to develop the basis to reconcile individual freedom with state authority, common interests and general will of the people (Locke, 1689; Rousseau, 1762). Within the field of translational science, the renewed "social contract" refers to a much more limited notion of renewed agreement and cooperation surrounding the goals of science (Maienschein et al., 2008).

6 For more information on expected well-being Pierson and Millum (2018) refer to Sharp and Millum (2018).

7 Institutional Review Boards evaluate the ethics of human subject research. They are also sometimes called Research Ethics Committees or Research Ethics Boards, particularly outside of the US.

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Author contributions

EMRS, SM, and ET developed the original idea and outline for this manuscript. All authors (EMRS, SM, JSF, ET) collaborated on idea development, drafting, critical revision, and final approval of the research. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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